ATTRIBUTION OF LUNG CANCER TO ASBESTOS EXPOSURE IN MINERS IN SOUTH AFRICA

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Master of Science in Medicine in the field of Epidemiology and Biostatistics

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DECLARATION

I, Shobna Chauhan declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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10th day of May, 2005

In loving memory of my dad

Ghambhirsih Chauhan

(1946 – 1998)

Dedicated to my husband, mum and sister

PUBLICATIONS AND PRESENTATIONS

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ABSTRACT

An autopsy-based case-series of South African miners was used to evaluate the evidence required to attribute a miner's lung cancer to occupational asbestos exposure for compensation. The slightly different Helsinki (1997) and National Institute for Occupational Health (NIOH) criteria (1988) require that one of four factors (asbestosis, occupational exposure, raised burden of asbestos fibres and/or bodies) be fulfilled for attribution. These criteria were applied to the case-series to determine and compare the proportions of NIOH- and Helsinki-attributable lung cancers. Of 195 lung cancer cases, 47% (91) were Helsinki-attributable and 52% (101) NIOH-attributable: with 72% concordance. Some differences in the details of occupational exposure criteria and methods for assessing the burden of asbestos in the lung were responsible for differences in these proportions. If attribution had taken place using only presence of asbestosis and the occupational exposure history, many cases would not have been attributable to asbestos. Therefore, taking into account burden of asbestos in lung tissue was important. However, it was found that phase contrast microscopy (PCM) for counting asbestos bodies was "sufficient" and that scanning electron microscopy (SEM), advocated by the Helsinki criteria, added <1% of the cases, suggesting that the cost of expensive SEM fibre counts in a developing country may outweigh the benefits. Using the Helsinki criteria as the gold standard, the sensitivity of the NIOH criteria was 75.8% (95% CI: 65.7 – 84.2).

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GLOSSARY OF TERMS

AMPHIBOLE FIBRES

- Long, straight and rigid asbestos fibres (e.g. crocidolite and amosite)

ASBESTOS BODIES IN THE LUNG

- Asbestos fibre that is coated with protein and iron compounds in the lung

ASBESTOS FIBRES IN THE LUNG

- "naked" asbestos fibre that is the same as the inhaled particle

ASBESTOS-EXPOSED OCCUPATION

- An occupation in a mine with potential exposure to asbestos

ATTRIBUTION CRITERIA

- Conditions under which an individual's lung cancer can be considered related to occupational asbestos exposure

HELSINKI CRITERIA

- Attribution criteria as defined at an international experts meeting in Helsinki, Finland

HELSINKI-ATTRIBUTABLE

- Lung cancer cases considered attributable to asbestos exposure using the Helsinki criteria

LAG PERIOD

- Period between first exposure to asbestos and diagnosis of the lung cancer

MINER

- A person who has ever worked on any mine

NIOH CRITERIA

- Attribution criteria as defined by the NIOH in 1988

NIOH-ATTRIBUTABLE

- Lung cancer cases considered attributable to asbestos exposure using the NIOH criteria

PRIMARY EXPOSURE

- Exposed while working on an asbestos mine

SECONDARY EXPOSURE

- Exposed while working with asbestos-containing materials on a non-asbestos mine

SERPENTINE FIBRES

- Long curly asbestos fibres that are more easily broken down in the lung (e.g. chrysotile)

GLOSSARY OF ABBREVIATIONS

CCOD

- Compensation Commissioner for Occupational Diseases, Pretoria, South Africa

LM

- Light Microscopy at 400x magnification

MBOD

- Medical Bureau for Occupational Diseases, Johannesburg, South Africa

NIOH

- National Institute for Occupational Health, Johannesburg, South Africa

PCM

- Phase Contrast Light Microscopy at 400x magnification

SEM

- Scanning Electron Microscopy at 2000x magnification

SEM-EDS

- Scanning Electron Microscopy with Energy Dispersive Spectroscopy analysis

1.0 INTRODUCTION

1.1 History of asbestos mining and use in South Africa

South Africa has mined, used and exported all three major types of asbestos: chrysotile, amosite and crocidolite. Asbestos mining and production in South Africa peaked in 1977 with 380 000 tons being produced: making South Africa the third largest supplier of asbestos in the world[1]. By the mid-1980s South Africa was producing only about 160 000 tons, with almost 90% of the asbestos produced being exported[2]. Although all asbestos mining has now ceased, the last of the crocidolite mines in the Northern Cape only closed in 1996[3], and in 1998 20 000 tons of chrysotile were still used to manufacture building materials and pipes[1]. Because of the vast usage of asbestos in many materials used for insulation, cement, friction and other products, asbestos fibres have persevered in South Africa's mining environment.

1.2 Asbestos exposure in the South African mining industry

Miners may experience either primary or secondary exposure to asbestos which could have come from several different sources. Primary exposure occurs during asbestos mining. Secondary exposure occurs through dust generated from either using, fixing or constructing asbestos cement pipes, corrugated sheeting, electrical and heat-generating equipment insulated with asbestos, brake and clutch pads made of asbestos and any other asbestos containing products encountered during the mining process[4].

1.2.1 Asbestos-exposed occupations

Davies et al (1987)[5], Martin (2002)[6] and Rice et al (2003)[7] have determined and published occupations with potential exposure to asbestos, related to different working environments.

These three lists of occupations, presented in Table 1.1, correlate well with the constantly developing NIOH list of potential asbestos-exposed occupations in South African mines and works.

Table 1.1: Potential asbestos-exposed populations in different working environments

Author (year)	Working environment	Potential asbestos-exposed occupations
NIOH	South African mines and works	asbestos mine worker, boilermaker, carpenter, electrician, fitter and turner, furnace mason, loco driver, mechanic, painter, pipe fitter, plumber, welder, winch driver, winding engine driver, miner (diamond, manganese, copper or iron mine), and worker at electricity generating plants, works and smelters
Davies et al (1987)[5]	South African Gold mines	boilermaker, electrician, fitter, geologist, mason, mill shiftsman, pipe laying, pump repair and plumber
Martin (2002)[6]	All industrial sectors	asbestos miners, workers producing asbestos-containing products (e.g. fire bricks, fire-retardant paints, asbestos cement), boiler makers and repairers, brake lining workers, insulators, maintenance workers/millwrights, pipe fitters, power plant workers and shipyard workers
Rice et al (2003)[7]	All industrial sectors	asbestos miner, asbestos miller, furnace/boilermaker, carpenter, electrician, fitter, mechanic, painter, plumber, worker in power generation and welder/cutter/burner

As covered by the Occupational Diseases in Mines and Works Act of 1973, described in detail in Section 1.6

1.3 Asbestos fibres in the lung

Mining asbestos or working on asbestos-containing products releases asbestos fibres into the environment, and they are inhaled. In the lung, asbestos is found in two forms. The first is the fibre which is the same as the inhaled fibre[4]. Because this fibre has a narrow diameter it is very difficult to detect it under the light microscope, regardless of length. Fibres can be seen by phase contrast microscopy (PCM) but cannot be distinguished into asbestos and non-asbestos fibres (Table 1.2). Scanning electron microscopy (SEM) however, is more

sensitive in detecting smaller fibres, and when coupled with energy dispersive spectroscopy (EDS), asbestos fibres can be differentiated from other fibres[4] (Table 1.2).

The second form in which asbestos is present in the lung is the asbestos body: an asbestos fibre that has been coated with proteins and iron compounds in the lung. Asbestos bodies can be seen under the light microscope (LM) (Table 1.2), and have a transparent core, are most often straight and unbranched and are described as being "dumbbell" or "drumstick" shaped[4]. The non-specific term "ferruginous body" was previously used because other fibres may also be similarly coated. However, Churg and Warnock (1979) have shown that ferruginous bodies with the appearance of asbestos bodies almost always have an asbestos fibre core[8]. The ratio of asbestos fibres:asbestos bodies in the lung is variable and may range from 5:1 to 10 000:1[4] depending on fibre type and size.

Table 1.2: Use of LM, PCM and SEM to count fibres, asbestos fibres and asbestos bodies [4,9]

Counts	Microscopy method		
	LM	PCM	SEM
Fibre	-	+	++
Asbestos fibre	-	-	++ (EDS)
Asbestos body	+	++	-

Key:
- \- not recommended
- \+ recommended, not optimal
- ++ recommended, optimal

EDS Energy Dispersive Spectroscopy

1.4 Asbestos-related lung diseases

Asbestos can cause a number of pathological changes in the lung and their development depends largely on the exposure intensity. The association between lung cancer and exposure to asbestos was described as early as 1955 by Sir Richard Doll and has subsequently been confirmed in numerous different epidemiological and experimental studies, as comprehensively reviewed in Craighead (1982)[4], Churg (1998)[9] and the Helsinki report[10]. This relationship is summarised as follows: "The relative risk of lung cancer is

estimated to increase 0.5 – 4% for each fibre per cubic centimetre per year (fibre-years). With the use of the upper boundary of this range, a cumulative exposure of 25 fibre-years is estimated to increase the risk of lung cancer two-fold"[11]. All four major histological cell types (small cell, large cell, adeno and squamous) of lung cancer are associated with asbestos exposure and the location of the cancer in the lung is not specific to asbestos exposure[11]. The pathological features and clinical signs and symptoms of asbestos-associated lung cancers are indistinguishable from those caused by other factors[11].

Asbestosis, a diffuse interstitial fibrosis caused by asbestos, requires heavy exposure and develops 15-20 years after the first exposure[6,12,13]. Whether asbestosis serves as a precursor or a marker of asbestos-related lung cancer has yet to be resolved[14-18], but the increased risk of lung cancer in asbestosis cases has been accepted by the scientific community[10].

Mesothelioma, a cancer of the pleural membrane, is associated with asbestos exposure[19] but requires a far lower cumulative dose of asbestos[11] and its development is not associated with that of asbestos-related lung cancer. Pleural plaques, a scarring of the pleural membrane, are strongly associated with asbestos exposure, and often require only low levels of asbestos exposure to develop[11]. These can occur along with lung fibrosis or lung cancer or independently[6,11-13,19]. Benign pleural effusions and chronic airflow limitation are associated with but not specific to asbestos exposure[6,12,13,19].

1.5 Lung cancer in miners

Miners in South Africa are exposed to several potential risk factors for the development of lung cancer, both occupational and non-occupational. Occupational carcinogens include: respirable dust with high concentrations of crystalline silica, radon daughters, diesel fumes,

arsenic, cadmium, nickel and asbestos[9], while the most important non-occupational carcinogen is cigarette smoke[6]. These carcinogenic exposures may occur separately or in combination (mixed exposures). Some mixed exposures may lead to a multiplicative effect on the risk of dying from lung cancer: Hammond *et al* (1979)[20] showed that, compared to non-smokers with no asbestos exposure, the risk of dying of lung cancer was 5 times higher in non-smokers exposed to asbestos, 10 times higher in smokers not exposed to asbestos and 50 times higher in smokers exposed to asbestos[9,20].

1.5.1 Asbestos fibre length, type and carcinogenicity

After exposure to asbestos, the risk of developing lung cancer is influenced by the length and type of asbestos fibre inhaled, which influences fibre retention in the lung[11]. Asbestos fibre length affects fibre retention because relatively short asbestos fibres tend to be removed from the lung via macrophage phagocytosis and emigration, while longer fibres cannot be phagocytosed[9]. Asbestos fibre type influences fibre retention because amphibole fibres (crocidolite & amosite) are relatively straight and broad fibres that do not fragment easily and are chemically stable in the lung[9] thereby limiting clearance from the lung. Serpentine fibres (chrysotile), on the other hand, tend to fragment into straight, short small fibres that lack durability and are chemically unstable in the lung[9]. This leads to faster clearance rates or chemical decomposition, resulting in lower asbestos fibre retention in the lung. These inherent structural differences between the two fibre types, led to the evolution of the "amphibole hypothesis" which led many to assume a lesser concern in the use of serpentines than for amphiboles. But, a study by Stayner et al (1997)[21] showed a 'strong exposure-response relation between exposure to chrysotile asbestos and mortality from lung cancer' and reviews by Stayner (1996)[22] and Nicholson (2001)[23] both concluded that the risk of lung cancer does increase on exposure to chrysotile. It is therefore imperative to treat

serpentine asbestos with the same concern as amphibole asbestos, in terms of its ability to induce disease, despite differences in lung fibre retention.

Many studies have thus far only investigated the risk of lung cancer in asbestos-exposed **populations** but have not looked at criteria for attributing an **individual's** lung cancer to asbestos exposure[24,25]. This becomes important for worker's compensation processes.

1.6 Compensation of asbestos-related lung cancer to miners in South Africa

The Occupational Diseases in Mines and Works Act 78 of 1973 (ODMWA, 1973)[26], provides for compensation, to individuals, for asbestos-related lung cancer, caused by occupational exposure in mines and scheduled works[26].

This Act provides for autopsies for all miners and ex-miners and, provided the next of kin agrees, the last attending doctor has to remove the cardio-respiratory organs, and submit them for pathologic examination. The Pathology department at the NIOH conducts these examinations, to determine the presence of occupational lung disease and submits their findings to the Medical Bureau for Occupational Diseases (MBOD). The MBOD convenes certification committee meetings which review the autopsy findings together with the work history and come to a decision as to whether the disease can be certified as compensable. The Compensation Commissioner for Occupational Diseases (CCOD) determines the compensation amount and manages the payment of the benefit to the deceased's family[26,27].

Because miners may be exposed to a number of potential carcinogens both occupational and non-occupational (e.g. cigarette smoke), criteria for determining whether in an individual's

case the lung cancer should be attributed to occupational asbestos exposure is necessary to determine compensability of the disease.

1.7 Attribution of lung cancer to occupational asbestos exposure

The conditions under which an individual's lung cancer can be considered to be related to occupational asbestos exposure are referred to as attribution criteria. These criteria are necessary to clarify the conditions required to determine occupational asbestos exposure and how it should be measured, in order to facilitate the compensation process.

1.7.1 Helsinki Criteria for the attribution of lung cancer to asbestos exposure

In 1997, the International Experts Meeting on Asbestos, Asbestosis and Cancer convened in Helsinki and developed a Consensus Report titled "Asbestos, asbestosis and cancer: the Helsinki criteria for diagnosis and attribution"[11] (the Helsinki criteria). The experts, from eight non-asbestos producing countries, included pathologists, radiologists, occupational physicians, pulmonary physicians, epidemiologists, toxicologists, industrial hygienists and laboratory specialists in tissue fibre analyses. This Consensus Report is supported by the more comprehensive Research Report[10] (Helsinki report) which details the proceedings of the meeting and supplements information in the Consensus Report. The Helsinki criteria suggest both quantitative and qualitative factors for attributing lung cancer cases to occupational asbestos exposure: workplace dust measurements or cumulative fibre dose; presence of asbestosis; an occupational history of asbestos exposure; evidence of a raised burden of asbestos bodies in the lung; evidence of a raised burden of asbestos fibres in the lung[11]. Accurate workplace dust measurements or cumulative fibre dose, both quantitative measures, are historically not available worldwide, cannot be determined retrospectively and if they were done it is very difficult to get hold of them. In the absence of these, the other

above-mentioned measures become useful as proxies for the unknown quantitative exposure assessments.

1.7.2 NIOH criteria for the attribution of lung cancer to asbestos exposure

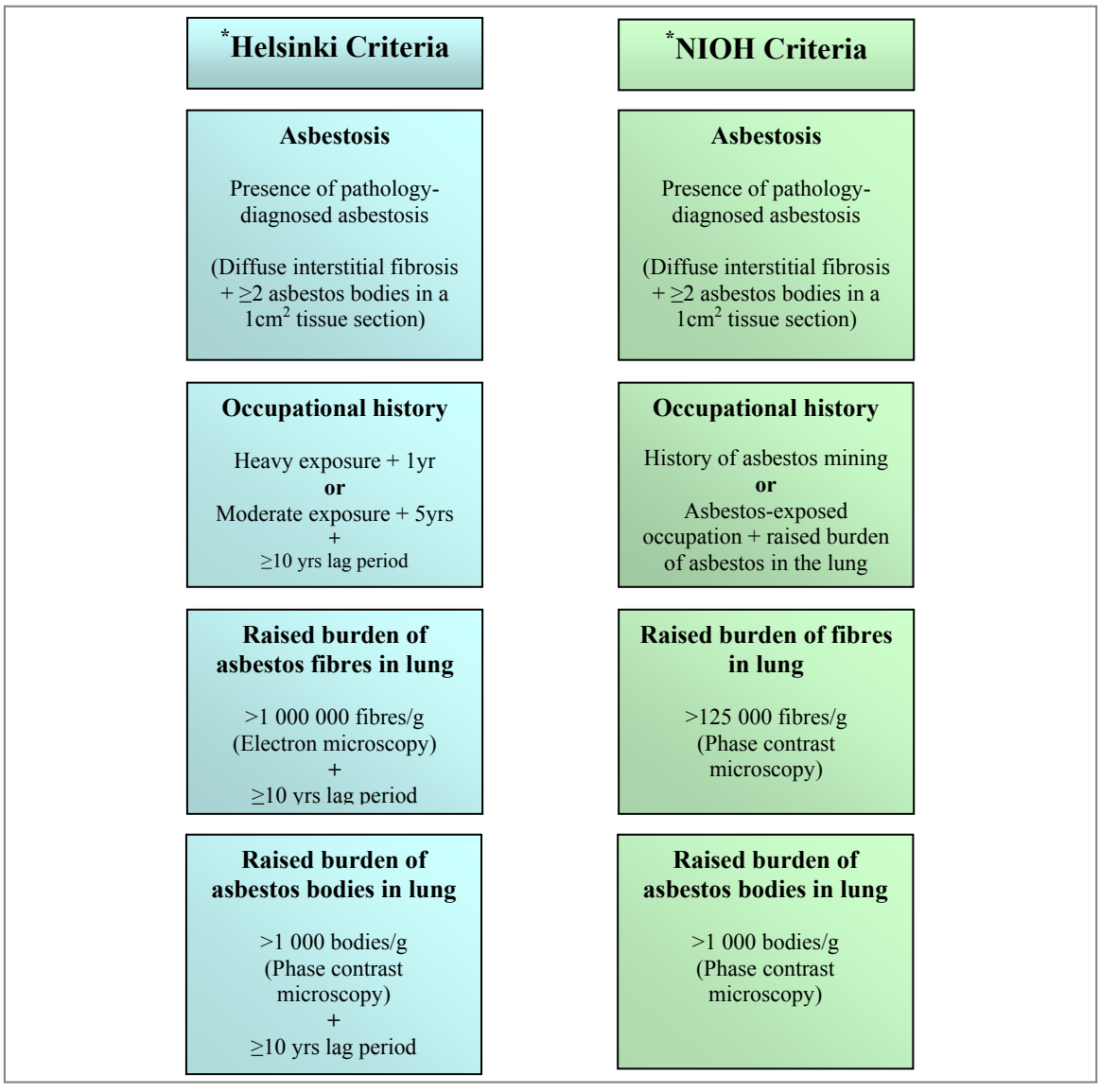
Since about 1988, the NIOH in response to the ODMW Act, had already developed and implemented a set of criteria to estimate an individual's occupational asbestos exposure and thereby attribute a lung cancer to asbestos exposure. These criteria include: presence of asbestosis; an occupational history of asbestos exposure; evidence of a raised burden of asbestos bodies in the lung; or evidence of a raised burden of asbestos fibres in the lung.

1.7.3 Comparison of the Helsinki and NIOH criteria for the attribution of lung cancer to asbestos exposure

The main difference between the two sets of criteria is that the NIOH criteria are specific for asbestos exposures in the mining industry while the Helsinki criteria may be applied to all industrial groups and were formulated from a developed world perspective.

Interestingly though, the two sets of criteria do apply similar factors of attribution with some differences in the conditions within these factors, as shown in Figure 1.1. Firstly, only the Helsinki criteria require that all cases have a 10-year lag period between the time of first known exposure to asbestos and diagnosis of lung cancer, in addition to other factors. Secondly, the NIOH criteria are specific in defining an occupational history of asbestos exposure, while the Helsinki criteria provide adaptable guidelines for determining asbestos-exposed occupations using burden and duration of exposure [10]. Thirdly, in addition to being employed in an asbestos-related occupation, the NIOH criteria require evidence of a raised burden of asbestos in the lung. The Helsinki Criteria, on the other hand, require an

occupational history that complies with the minimum exposure times specific to the occupational exposure category. Fourthly, to establish raised asbestos fibre concentrations, the NIOH criteria require a level of 125 000 fibres/g dry lung tissue (NIOH laboratory established reference value), on phase contrast microscopy, while the Helsinki criteria suggest a reference value of 1 000 000 fibres/g dry lung tissue, on scanning electron microscopy.



*Within each set of criteria, each block contains a factor and the condition defining it

Fig 1.1: Comparison of Helsinki [10,11] and NIOH criteria for the attribution of lung cancer to occupational asbestos exposure.

On the effect of smoking on the development of lung cancer, the Helsinki Criteria state: "while smoking does influence the overall risk of developing lung cancer, this effect does not detract from the risk of lung cancer attributable to asbestos exposure"[11]. South Africa's compensation legislation also doesn't take smoking into account in determining whether an individual's lung cancer was caused by asbestos[26]. Therefore the effect of smoking will not be taken into account in the attribution process in this study.

1.8 Critical review of studies using the Helsinki criteria

Subsequent to the publication of the Helsinki Criteria, several studies have been conducted to determine the attribution of lung cancers to asbestos exposure. The objectives, criteria used and results of four such studies are summarised in Table 1.3, and discussed below.

In addition to determining the proportion of lung cancer cases attributable to asbestos exposure by employing the Helsinki criteria, Bianchi *et al* (1999)[28] showed that a similar proportion of cases also had either moderate or large pleural plaques (Table 1.3), and thereby suggested that using the size of pleural plaques to determine attribution may yield results similar to those obtained using the Helsinki criteria and that the size of pleural plaques be used as a risk indicator for lung cancer. This suggestion contradicts the Helsinki criteria which states that the presence of pleural plaques alone may not be used for attribution purposes[11]. While this study did show that the percentages of Helsinki-attributable cases (61%) and cases with pleural plaques (58.7%) were similar, no attempt was made to determine the sensitivity of using pleural plaques to determine attribution compared to using the Helsinki criteria. Necropsy cases with lung cancer were selected over an 18-year period; methods may have therefore been compromised in terms of case selection, exposure assessments and inter-observer variation.

Table 1.3: Summary of methods and results of studies conducted to determine the attribution of lung cancer cases to asbestos exposure

Author, year	Objectives	Population	Criteria employed	Summarised results	Other points

Bianchi *et al*[28], 1999 (Italy)	To determine the proportion of lung cancers attributable to asbestos in the Monfalcone area (Italy)	Hospital necropsy cases identified over a period of ~18 years. (N=414)	• Asbestosis
			• Occupational history
			  • heavy or moderate exposure according to the Helsinki Criteria
			• Presence of ABs
			• Pleural plaques:
			  • Graded into Class 1-3
				% of cases attributable using each of the criteria:
				• 24.7% - AB concentration > 10 000AB/gdw
				• 31.0% - AB concentration > 5 000AB/gdw
				• 58.7% - Class 2 & 3 pleural plaques
				• 61.0% - Helsinki criteria for occupational history and asbestos body concentration (criteria not clearly stated by authors)
					While these cases were from the general population, most of the men had ever worked at the Monfalcone shipyards during their lifetimes.

Mandi *et al*[29], 2000 (Hungary)	To determine the frequency of lung cancer patients occupationally exposed to asbestos To determine the number of tumours associated with asbestos	Lung cancer cases selected from a TB and Pulmonology Institute over a 3-year period (N=297)	• Occupational history (translated into fibre-years of exposure) • Asbestosis • AB counts on 25 cases	• ~86 cases were possibly occupationally exposed to asbestos • 11 (4%) cases had >25fibre-years of exposure and were therefore definitely exposed • Using the 4% attribution fraction, ~150 asbestos-related lung cancer cases could be expected per year	Fibrosis ≠ Asbestosis Fibrosis assessed using X-ray and HRCT were compared: HRCT found to be more sensitive. But results were not used in the attribution process: asbestosis could not be confirmed.
Roggli *et al*[30], 2000 (USA)	To investigate the asbestos content of lung tissue in a series of patients with lung cancer and some history of asbestos exposure	Lung cancer cases in author's consultation files, for which tissue asbestos analysis had been performed. (N=234)	• Asbestosis • Pleural plaques • Asbestos fibre burden • Occupational history • 3 groups: Group I – Asbestosis Group II – Pleural plaques; no asbestosis Group III – No pleural plaques; no asbestosis.	• 82% of lung cancer cases had asbestosis • 6.5% had a high fibre burden, an occupational history of asbestos exposure, but no asbestosis. • Asbestosis cases had a higher fibre burden than non-asbestosis cases and cases with pleural plaques had higher burdens than those with neither asbestosis nor pleural plaques. • Amphibole fibre burden sufficient to cause lung cancer is often accompanied with asbestosis.	This study did not attempt to perform an attribution as such, but rather looked at the asbestos content in lung tissue of lung cancer cases and attempted to correlate this with the diagnosis of asbestosis.
Mollo *et al*[24], 2002 (Italy)	To conduct a pathologic assessment of the prevalence of asbestos-related carcinomas using asbestosis	Lung cancer cases selected after either a pneumonectomy or lobectomy over a 6-year period. (N=924)	• Asbestosis • AB concentration • Occupational history on all asbestosis cases only	• 12.6% had raised AB concentrations • 6% had asbestosis • Using a 6% attribution fraction, ~2000 lung cancer cases per year should be asbestos-related in Italy	6% fraction of asbestos-attributable cases is similar to results from other population studies conducted in USA and Scotland.

Also, because of the inherent nature of a necropsy study using next-of-kin interviews to retrospectively collect occupational histories of the deceased, both information and recall bias may have played a role in data collection. Furthermore, the authors admit to varying degrees of reliability of their sources of exposure information: occupational histories are difficult to classify into heavy and moderate categories because of circumstances that differ between regions and within industries and occupations; and the use of asbestos bodies to reflect past asbestos exposure is unreliable because of the fast clearance rates observed with chrysotile fibres[28]. Moreover, although it was stated that asbestosis was diagnosed in cases, no data are presented, nor is it stated that asbestosis was used in the application of the Helsinki criteria. Consequently, while the Helsinki criteria were used to answer the study question, insufficient information was provided on the methods used to apply these criteria and thereby derive the fraction of asbestos-attributable lung cancer cases.

The article by Mandi *et al* (2000)[29] differed from that of Bianchi *et al* (1999)[28]; in applying the Helsinki criteria it addresses the issues of "improvement in assessment of individual asbestos exposure" and "correlation between job-exposure data and the asbestos fibre burdens of the lungs in relation to various asbestos-related disorders"[29]. Individual exposure assessments were conducted using an internationally accepted questionnaire which allowed work histories to be translated into cumulative asbestos exposures expressed in fibre-years using a standard method. Applying a level of 25 fibre-years to determine occupational exposure to asbestos, as suggested by the Helsinki criteria, 4% of the lung cancers were due to asbestos exposure in the workplace (Table 1.3)[29]. But, this percentage may have been higher if other parameters, which were measured in this study, were also used to assess individual asbestos exposure such as presence of asbestosis and raised burdens of asbestos bodies in the lungs. This weakness in the study is demonstrated by the effort put into

diagnosing asbestosis by both x-ray and HRCT (high resolution computed tomography) and then not using these results in the attribution process. Furthermore, of the 25 patients who had lung tissue specimens examined for asbestos bodies, 6 (24%) had raised concentrations (> 0.2million fibres/g dry tissue) of chrysotile fibres[29] (Table 1.3). By the Helsinki criteria, these levels of raised fibre concentrations are an indication of significant asbestos exposure and should be used in the attribution process[11]. Of further interest are the 30 patients in the non-exposed group who had evidence of either fibrosis or pleural plaques but did not appear to be further investigated. While no selection bias was evident in the cases selection process, the use of questionnaires to collect retrospective work histories may have introduced an element of recall and/or information bias which may have lead to misclassification of exposure.

While Roggli *et al* (2000)[30] did not attempt an attribution of lung cancers to asbestos exposure *per se*, they did examine most of the parameters suggested by the Helsinki criteria: presence of asbestosis, presence of pleural plaques, asbestos burden in the lung; and occupational history (Table 1.3). The 82% of lung cancer cases diagnosed with asbestosis is largely a reflection of the selection bias introduced through case selection criteria which included lung cancer cases that were medicolegal referrals for asbestos litigation and cases on which asbestos fibre analyses had already been performed. The group of cases with asbestosis had a significantly higher median concentration of asbestos bodies and fibres in the lung resulting in the suggestion that "an amphibole fibre burden sufficient to induce carcinoma of the lung is most often (but not invariably) accompanied by histologic evidence of asbestosis"[30]. But, in cases with neither asbestosis nor pleural plaques the ranges of asbestos fibres (370-157 000 fib/g wet tissue) and bodies (2.6-45 800 AB/g wet tissue) overlapped with the ranges of asbestos fibres (14 600-8 540 000 fib/g wet tissue) and bodies

(150-343 000 AB/g wet tissue) in cases with asbestosis[30]. This finding has impact for cases with no evidence of asbestosis or pleural plaques but who do have high asbestos fibre burden in the lung; by the Helsinki criteria most of these lung cancer cases should be asbestos-attributable. A limitation of this study is that fibre burden analyses do not accurately reflect past exposure to chrysotile asbestos due to clearance rates and digestion of these fibres within the lung[30]. The use of patient or next-of-kin interviews to collect retrospective occupational exposure information may have introduced an element of recall and information bias which could lead to misclassification of exposure. This misclassification may have been exacerbated by the lack of information on intensity or regularity of exposure.

Mollo *et al* (2002)[24] used the presence of asbestosis and the concentration of asbestos bodies per gram of dry weight, to determine the attribution of lung cancers to asbestos exposure. Of the 924 cases of lung cancer, 6% (54) were judged to have asbestos-related lung cancer because of the presence of asbestosis (Table 1.3). But, even though a further 62 lung cancer cases had >1000 asbestos bodies/g dry tissue, which is considered sufficient to identify persons with a high probability of occupational exposure to asbestos by the Helsinki criteria, they were not considered asbestos attributable. In fact, the concentration of asbestos bodies by light microscopy was used mainly to prove that these counts can be taken into account along the diagnostic path in the detection of asbestosis in a fibrotic lung. In using only asbestosis to determine the prevalence of asbestos-related lung cancers, it was estimated that ~2000 cases of lung cancer per year should be asbestos-related[24]. This may have been much higher had the Helsinki criteria been used, where cases with either asbestosis, asbestos body burdens in excess of 1000 bodies/g dry tissue or occupational histories of heavy or moderate exposure were also considered.

While the populations considered in these four studies (Table 1.3) were different resulting in different proportions of asbestos-attributable cases, they demonstrated: the difficulty in obtaining reliable proxy measures of exposure using questionnaires and next-of-kin interviews; the practical limitations of applying all criteria to determine attributability and the using one parameter of the Helsinki criteria may underestimate the number of lung cancers that are asbestos-attributable.

1.9 Contribution to current body of knowledge

This study will add to the body of literature by providing the most comprehensive application of the Helsinki criteria to date because all possible factors within the Helsinki criteria will be utilised to determine the proportion of asbestos-attributable lung cancers in South African miners. The corresponding proportions of asbestos-attributable lung cancer cases from the Helsinki and NIOH sets of criteria, one established in South Africa in 1988 (NIOH criteria) and the other established by international experts in 1997 (Helsinki criteria), will be compared.

1.10 Study question

For compensation purposes, what criteria are considered adequate for attributing an individual's lung cancer to occupational asbestos exposure, regardless of exposure to other potential carcinogens?

1.10.1 Aims

To determine the respective proportions of lung cancers in South African miners which are attributable to asbestos exposure by applying the Helsinki and NIOH criteria.

From a comparison of these proportions, to construct a practical, economical algorithm for determining whether occupational asbestos exposure contributed significantly to the development of lung cancer.

1.10.2 Objectives

1. To determine the proportion of lung cancer cases in miners, diagnosed at autopsy by the NIOH, attributable to occupational asbestos exposure based on the Helsinki criteria.
2. To determine the proportion of lung cancer cases in miners, diagnosed at autopsy by the NIOH, attributable to occupational asbestos exposure using the NIOH criteria.
3. To assess the level of agreement between the NIOH and Helsinki criteria in assigning asbestos-attributability of lung cancers in miners in South Africa.
4. To measure the correlation between phase contrast and scanning electron microscopy-detected concentrations of asbestos fibres and asbestos bodies.
5. To identify possible predictors of SEM-determined raised asbestos fibre concentrations in the lungs of South African miners.
6. To create an algorithm that can be recommended for assessing asbestos-attributability of lung cancer in South African miners.

2.0 Methods

2.1 Study population

This comprised all deceased South African miners and ex-miners whose cardio-respiratory organs were autopsied at the NIOH from January 2000 to December 2002 (N=7655). The study period was selected to assure a manageable number of specimens for scanning electron microscopy.

2.2 Study design

This was a descriptive case-series of all cases in the study population with lung cancer diagnosed at autopsy. The design was chosen because the nature of the study question did not require the calculation of any measures of association.

2.3 Lung cancer case definition

A histologically proven cancer of primary origin in the lung. The histological cancer cell types included in this study were: large cell, small cell, adeno- and squamous carcinoma. Where the lung cancer cell type was not stated, diagnoses of either lymphoma or Kaposi sarcoma were excluded and the case was included in the series. Where there was a clinical diagnosis of lung cancer and no lung cancer was found at autopsy, cases with evidence of radiation fibrosis or surgical removal of a cancer diagnosed during life, were included.

2.4 Data sources

2.4.1 Autopsy database

Pathology results of all autopsies performed at the NIOH are recorded onto the PATHAUT (PATHology AUTomated) database[27]. The database contains over 300 variables and 23 relevant variables were used for this study. These included demographic details, mining history and pathology findings related to lung cancer and asbestosis.

2.4.2 Fibre Count database

Routine phase contrast and non-routine electron microscopy results of all lung specimens submitted for fibre analysis are recorded on the fibre count database, which was originally recorded onto a MS Excel spreadsheet. To create a well established database environment, all data were imported into Epi-Info 2000 and a data entry view was created including data checks, limits and drop-down lists to facilitate quick and accurate data entry. Demographic data and concentrations of asbestos bodies and fibres were extracted from this database.

2.4.3 Pathology Examination Booklet

Detailed occupational and smoking histories are not captured onto the Autopsy database so cases' "Pathology Examination Booklets" (a paper record), were used to obtain this information.

2.5 Selection and review of lung cancer cases

The fibre count database was used to identify lung cancer cases within the defined study period. Cases with either a clinical or pathology cause of death of lung cancer were selected for review by a principal pathologist (Dr J Murray). Comparing lung cancer cases found on the fibre count database to those on the autopsy database revealed that 23 lung cancer cases that fulfilled the definition of a case did not have lung tissue submitted at the time of autopsy for fibre counts. These cases were excluded from the study. This resulted in 195 lung cancer cases being included in the study.

2.6 Sampling

Since the lung cancer case-series was of a manageable size (N=195), no sampling strategy was employed and all eligible cases were included in the study.

2.7 Database development

2.7.1 Database merge

The autopsy and fibre count databases were merged in Epi-Info 3.2 (February 2004), using patients' unique "pnumbers". Then smoking and detailed occupational histories were manually entered onto the database. A complete list of the merged database variables with a description of each variable and its source is appended (Appendix A).

2.7.2 Database cleaning

All data cleaning was performed in Epi-Info 3.2.

Missing values – frequency checks were performed on all variables to determine the extent of missing values in the database. All case records were reviewed to ensure that data were actually not available as opposed to not recorded. All "missing" data that could be located were entered onto the database for completeness.

Logic checks – these are built into the autopsy database. All calculations on the fibre count database had been done on a hand-held calculator and were verified to ensure correct data entry. Manually entered occupational history information was also cross-checked to ensure logical data entry.

2.7.3 Data coding

In order to facilitate data analysis, most raw data variables require further manipulation and/or grouping resulting in the creation of new database variables. Data was exported from Epi-Info3.2 to Stata 8.0, via StatTransfer 7.0, to facilitate higher level coding and manipulation of data. Several secondary variables were created to describe occupational histories and exposures to asbestos. These are described in more detail in section 2.8.

2.8 Variables for assessing attributability

The variables for assessing attributability are described in order of their strength of association to an asbestos-attributable lung cancer.

2.8.1 Asbestosis

The presence of histologically confirmed asbestosis was diagnosed by means of the identification of diffuse interstitial fibrosis in conjunction with the presence of two or more asbestos bodies (using light microscopy) within a 1cm^2 tissue section.

2.8.2 Occupational history

2.8.2.1 For descriptive and statistical analyses

Table 2.1: Allocation of occupations to asbestos exposure categories

Exposure Category	Occupation or Industry causing asbestos exposure
Definite exposure	Any occupation on an asbestos mine.
Probable exposure	Boilermaker, carpenter, loco driver, electrician, furnace mason, winding engine driver, mechanic, painter, fitter and turner, pipe fitter, plumber, welder, winch driver.
Possible exposure	Miners on diamond, manganese, copper or iron mine. Persons employed at electricity generating plants, works and smelters.
Unlikely exposure	No evidence of exposure to any of the above-mentioned occupations or mine types
Unknown exposure	No occupational history available

For the purpose of all analyses, comprehensive occupational histories were used to allocate all cases into one of five exposure categories (Table 2.1). Briefly, all persons who had ever worked in any occupation on an asbestos mine had “definite exposure” to asbestos, all persons who worked in an asbestos-exposed occupation on a non-asbestos mine had “probable exposure”, all persons who ever worked on manganese, diamond, iron or copper

mines or at a works or smelter or in an electricity generating environment were considered to have had "possible exposure" to asbestos, and for the rest asbestos exposure was either "unlikely" or "unknown" due to insufficient occupational information.

2.8.2.2 For attribution purposes

For the purposes of attribution, occupational histories were evaluated and translated according to the Helsinki and NIOH criteria. The Helsinki report recommends face-to-face interviews supplemented with comprehensive employer records[10] to obtain a reliable history of occupational asbestos exposure which should then be translated into exposure categories. While face-to-face interviews could not be conducted on this case-series of deceased miners, a comprehensive occupational history, detailing occupation, period employed and mine types, was available for most miners. Table 2.2 shows the Helsinki guidelines[10] for the translation of occupational histories into asbestos-attributable exposure categories. However, these guidelines were designed to accommodate all industrial groups not just the mining industry, and as a result, modification of the recommended guidelines, which the Helsinki report allows, was effected to suit local occupations relevant to the South African mining industry (Table 2.2). These modified exposure categories were used in the Helsinki attribution process to determine attributability by occupational history.

Table 2.2: Translation of occupational histories into asbestos-attributable exposure categories, with modifications, as recommended in the Helsinki criteria[10]

Exposure category	Duration	Guidelines	Modified* requirements
Heavy exposure	>1yr	manufacture of asbestos products, asbestos spraying, insulation, demolition of old buildings	any occupation on an asbestos mine
Moderate exposure	>5yrs	construction, shipbuilding, heating trades, pipefitting, sheet metal work	boilermaker, carpenter, loco driver, electrician, furnace mason, winding engine driver, mechanic, painter, fitter and turner, pipe fitter, plumber, welder, winch driver

*Guidelines modified to suit occupations relevant to the South African mining industry

According to the NIOH attribution criteria, comprehensive occupational histories should be translated into the asbestos-attributable exposure categories described in Table 2.3. These were the exposure categories used in the NIOH attribution process.

Table 2.3: Translation of occupational histories into asbestos-attributable exposure categories, as recommended in the NIOH criteria

Exposure category	Occupation
Asbestos mining history	any occupation on an asbestos mine
Asbestos-exposed occupation	boilermaker, carpenter, loco driver, electrician, furnace mason, winding engine driver, mechanic, painter, fitter and turner, pipe fitter, plumber, welder, winch driver

2.8.3 Burden of asbestos in the lung

The burden of asbestos in lung tissue of deceased miners was determined by both phase contrast and scanning electron microscopy. Lung tissue sampling and processing, asbestos counting and relevant equations are described in detail in Appendix B. The conditions required for determining raised asbestos burdens in the lung for both the NIOH and the Helsinki criteria are provided in Table 2.4. For the Helsinki criteria, these levels of raised asbestos fibre or body concentrations are said to be sufficient to identify cases with a high probability of exposure to asbestos dust at work[11].

Table 2.4: NIOH and Helsinki criteria for raised concentrations of asbestos bodies and fibres

Asbestos	NIOH criteria		Helsinki criteria	
	Raised concentration	Microscopy method	Raised concentration	Microscopy method
Fibres	>125 000 fibres (≥5µm)	PCM	>1 000 000 asbestos fibres (≥1µm)	SEM
Bodies	>1000	PCM	>1 000	PCM

Reported as fibres/g dry lung tissue
Reported as bodies/g dry lung tissue

2.9 Application of the Helsinki and NIOH attribution criteria

Both sets of criteria were applied to each case. Factors within each set were applied according to their order on the flow chart (Fig 2.1). Thus, using the NIOH criteria, if a case met the criterion for the presence of asbestosis, it was judged attributable. If not, the next criterion was applied and so forth. This hierarchical algorithm was designed according to the strength of the association of the factor to an asbestos-attributable lung cancer[11], ease of application and resources available. The 10-year lag period, required by the Helsinki criteria, was not applied to cases as these were difficult to establish when no occupational history of asbestos exposure was indicated.

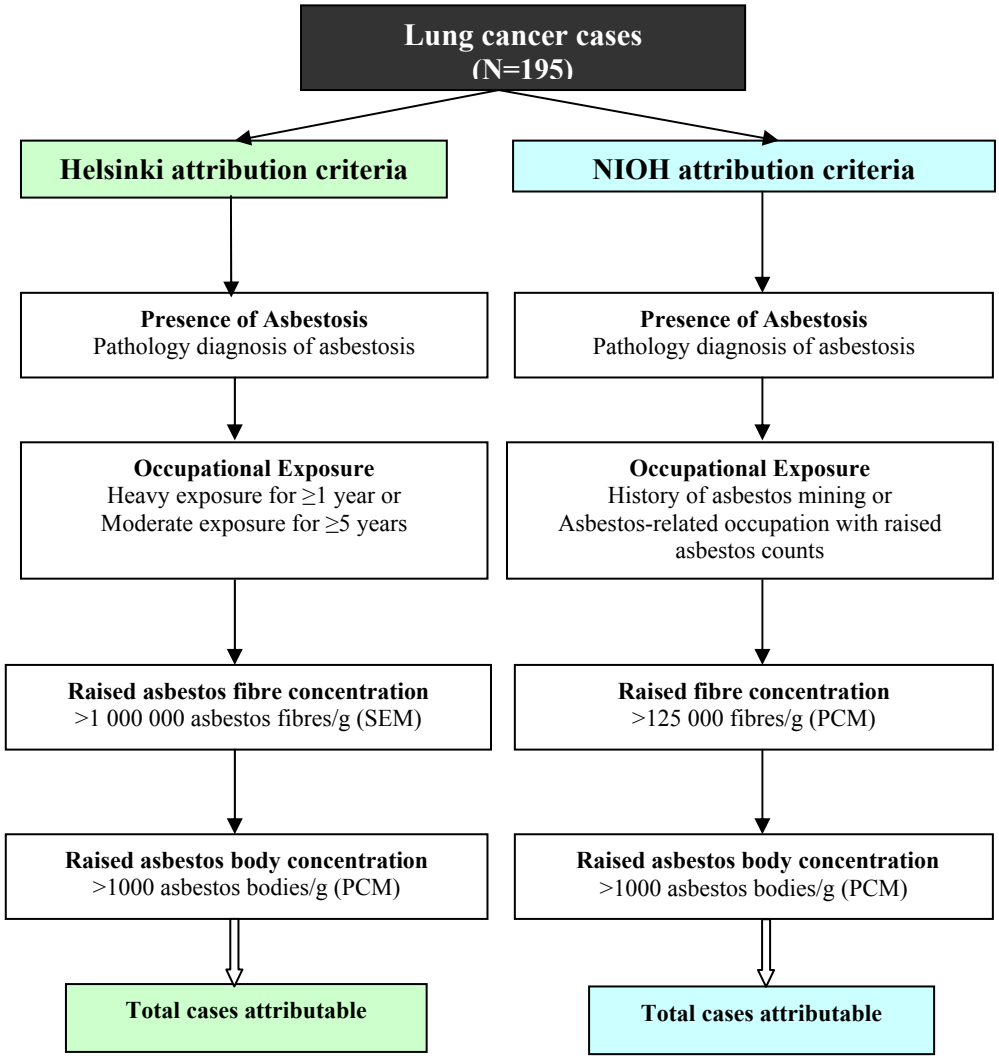


Fig 2.1: Application of the Helsinki and NIOH criteria to 195 lung cancer cases, using a hierarchy system

2.10 Statistical analyses

All data analyses were performed in Stata 8.0

Analysis of data included:

1. Descriptive frequencies of the distribution of lung cancer cases by year of diagnosis, age, smoking history, mining exposure and pathology findings;
2. Student's t-test for significant difference in mean age of black and white miners;
3. Distribution of asbestos fibre and body concentrations using normal density plots;
4. Comparison of the distributions of asbestos fibres and bodies by exposure groups using the non-parametric Wilcoxon rank sum test;
5. Comparison of phase contrast (PCM) and scanning electron microscopy (SEM) results using the Wilcoxon matched-pairs sign rank test;
6. Pearson correlation co-efficient between log-transformed PCM- and SEM-determined asbestos fibre and body concentrations;
7. Statistical comparison of the two sets of attribution criteria using tests of sensitivity and specificity with 95% exact binomial confidence intervals;
8. Kappa test of inter-observer agreement between the two methods of attribution;
9. Determination of predictors of SEM-determined raised asbestos fibre counts (eg. pathology findings, PCM asbestos body concentrations, occupational history, etc) using multiple logistic regression modelling.

2.11 Ethical clearance

The Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg provided ethical clearance for this study (Protocol number M03-07-05) on the 30th September 2003.

3.0 RESULTS

3.1 Descriptive analyses on 195 lung cancer cases

3.1.1 Demographic and smoking characteristics

Confirmed primary lung cancers (N=195) identified at autopsy over the 3-year study period constituted 2.2% of autopsy diagnoses in 2000[31], 1.9% in 2001[32] and 3.7% in 2002[33]. White miners constituted 74% (145) of this case-series, followed by black (22%) and coloured (5%) miners (Table 3.1). A significant difference of 15 years in the mean age at death between black and white miners (P<0.01) was observed and the frequency of cases increased with increasing age in white miners, but not in black miners. Smoking histories were available on 45% of the cases, of whom 93% had ever smoked (Table 3.1).

Table 3.1: Distribution of age and smoking status, by population groups

Population characteristics	Population group*			
	White (N=145)	Black (N=43)	Coloured (N=9)	Total
Age at death**				
Median	68	50	64	
Mean ± SD	67.4 ± 9.98	51.97 ± 9.77	70.11 ± 10.94	
Min	28	37	59	
Max	87	76	87	
Age groups**				
<40	1	3	0	4
40-49	6	16	0	22
50-59	18	11	1	30
60-69	56	6	4	66
≥70	61	3	4	68
Smoking status				
Never smoked	4	1	0	5
Ever smoked	77	2	3	82
No smoking status indicated	61	40	6	107

*Of 195 cases: 1 case had no population group information available
**Of 195 cases: 5 cases had no age information available

3.1.2 Distribution of cases by occupational exposure history

The distribution of cases by mine type (Table 3.2) shows that 32 cases had ever worked on an asbestos mine and 62 had ever worked on more than one type of mine; for 9 cases there was no information on mine type on their occupational history.

Table 3.2: Distribution of cases by mine type

Mine type	n	%N
Asbestos (n=32)		
Asbestos only	18	9.2
Asbestos + other (gold/platinum/coal/manganese)	14	7.2
Gold (n=121)		
Gold only	88	45.1
Gold and other(platinum/coal/tin/copper/iron/diamond/vanadium)	33	16.9
Platinum (n=14)		
Platinum only	12	6.2
Platinum and other (diamond/iron)	2	1.0
Other mine types (n=19)		
Coal only	6	3.1
Coal + other (iron/steel/industry)	3	1.5
Diamond only	3	1.5
Diamond + other (iron)	1	0.5
Iron only or manganese only or steel only	6	3.1
Unknown mine type (n=9)	9	4.6
Total (N)	**195**	**100.0**

The frequency of cases allocated to exposure categories (described in Table 2.1) based on mine type and occupation (Table 3.3) shows that less than half (47.2%) of the cases had evidence (definite or probable) of asbestos exposure, where 16.4% had definite exposure to asbestos. About 50% of the cases had no evidence of an asbestos-related occupation (unlikely exposure) and information on occupation was missing in 3.6% of the cases. Because some occupational histories may have been incomplete, the percentage of cases potentially exposed to asbestos at work could be underestimated.

Table 3.3: Frequency of cases per exposure category, based on occupation or industry causing the asbestos exposure

Exposure Category	Occupation or Industry causing asbestos exposure	n	%N*
Definite exposure	Any occupation on an asbestos mine.	32	16.4
Probable exposure	Boilermaker, carpenter, loco driver, electrician, furnace mason, winding engine driver, mechanic, painter, fitter and turner, pipe fitter, plumber, welder, winch driver.	44	22.6
Possible exposure	Miners on diamond, manganese, copper or iron mine. Persons employed at electricity generating plants, works and smelters.	16	8.2
Unlikely exposure	No evidence of exposure to any of the above-mentioned occupations or mine types	96	49.2
Unknown exposure	No occupational history available	7	3.6

*N=195

3.1.3 Pathology findings on cases

Table 3.4 presents the pathology findings, related to asbestos exposure, of lung cancer cases by exposure category. In total, asbestosis was identified in 6.7% and asbestos bodies in 15.4% of the cases, thus 17 cases had asbestos bodies (by light microscopy) but no asbestosis. The definite exposure category had a low proportion of cases (25%) with both lung cancer and asbestosis, whereas the unknown exposure category had ~43% of cases with both lung cancer and asbestosis.

Table 3.4: Prevalence of pathology findings of asbestosis, asbestos plaques and asbestos bodies by exposure category in lung cancer cases

Exposure category[a]	n[b]	Asbestosis n (%N)	Plaques n (%N)	Asbestos bodies[c] n (%N)
Definite	32	8 (25.0)	6 (18.8)	17 (53.1)
Probable	44	1 (2.3)	4 (9.0)	3 (6.8)
Possible	16	0 (0)	1 (6.3)	1 (6.3)
Unlikely/none	96	1 (1.0)	9 (9.4)	6 (6.3)
Unknown	7	3 (42.9)	2 (28.6)	3 (42.9)
Total	195	13 (6.7)	22 (11.3)	30 (15.4)

[a] Exposure categories described in Table 2.1
[b] Number of cases per exposure category
[c] Cases with asbestos bodies identified by routine light microscopy

3.2 Burden of asbestos fibres and bodies in the lung by PCM and SEM

A further measure of exposure is the burden of retained asbestos, in the form of fibres and bodies, in the lung. This was measured using both phase contrast microscopy (PCM) and scanning electron microscopy (SEM). Data for fibres and bodies are presented separately.

3.2.1 Asbestos fibres

On PCM 146 cases (75%) had any fibres detected and 76 (39%) had raised fibre concentrations (≥125 000 fibres/g dry tissue). SEM detected asbestos fibres in 51 cases (26%) and 8 (4%) had raised asbestos fibre concentrations (≥1000000 fibres/g dry tissue). This may be because SEM-EDS analysis was used to identify an asbestos component in the fibres whereas PCM does not allow for this (see Table 1.2).

Figure 3.1 shows, the distribution of fibre concentrations, determined by PCM. Fibre concentrations ranged from 0 to 4.8 million fibres/g dry lung tissue. A positively skewed distribution, is depicted by the normal density plot (red) on the histogram.

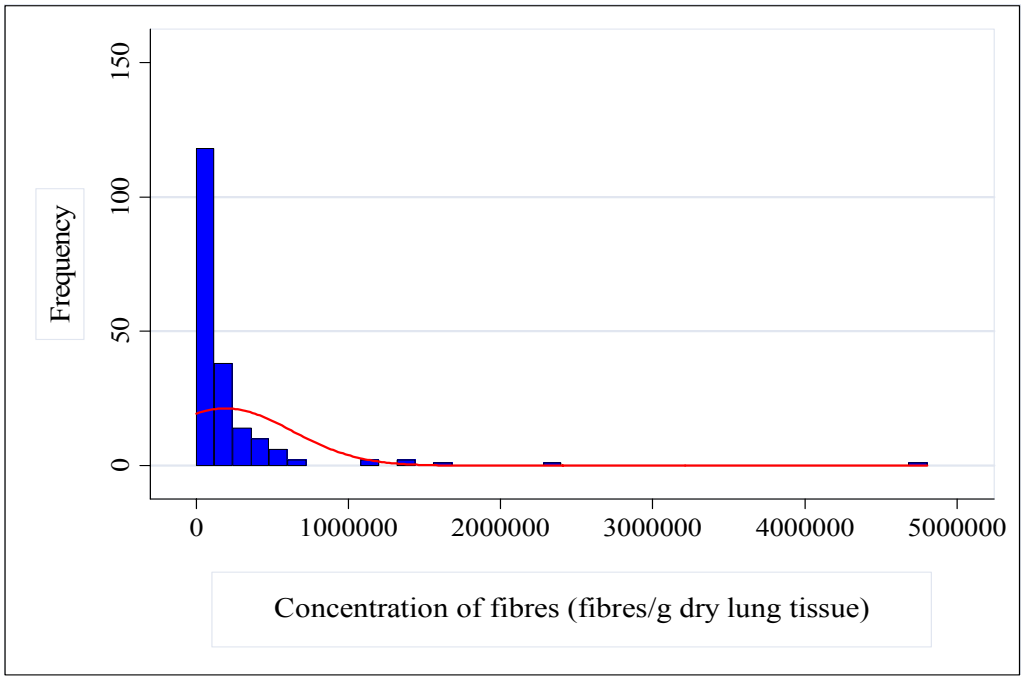


Fig 3.1: Distribution of concentrations of fibres, determined by PCM

Figure 3.2 shows the distribution of asbestos fibre concentrations by scanning electron microscopy (SEM) on the same 195 cases. Asbestos fibre concentrations ranged from 0 to 7.5 million fibres/g dry lung tissue. A positively skewed distribution with a wider spread of data, compared to PCM-determined concentrations, is depicted in Figure 3.2.

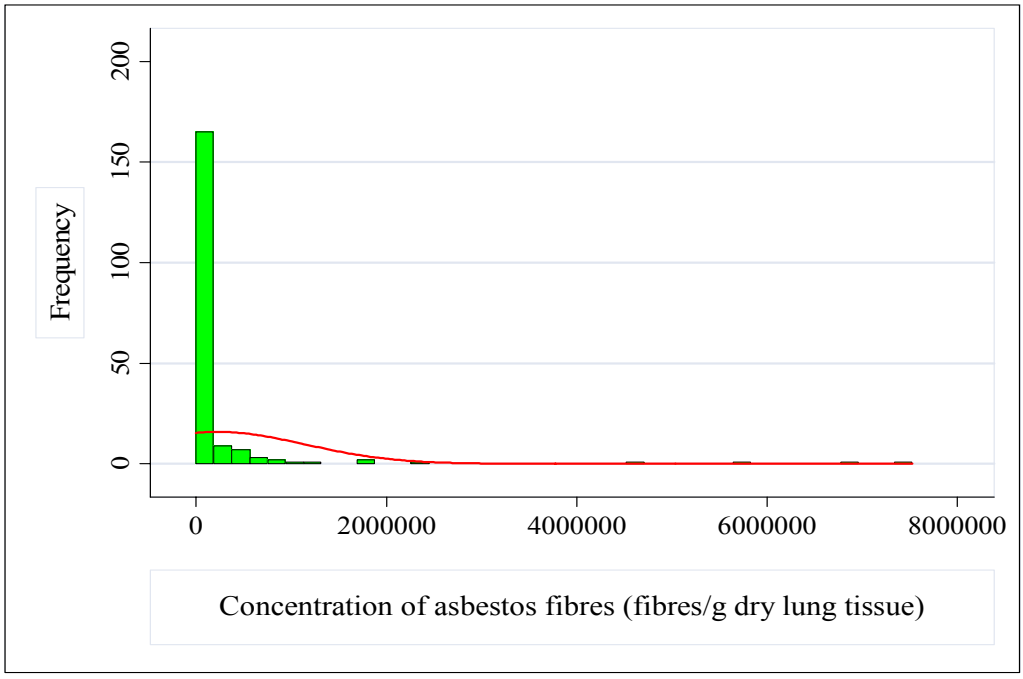


Fig 3.2: Distribution of concentrations of asbestos fibres, determined by SEM

Table 3.5 compares the distribution of fibre concentrations determined by PCM and SEM, by exposure category. For PCM analyses, cases with unknown occupational exposure had the highest median fibre concentration (389 887 fibres/g), followed by cases with definite occupational exposure (147 174 fibres/g). The median fibre concentration (Table 3.5), by PCM, of definitely exposed persons was thrice that of both possibly and probably exposed groups and twice that of the unlikely exposed group ($p<0.05$ for definite vs possible, definite vs probable and definite vs unlikely, using the non-parametric Wilcoxon rank sum test[34]). The difference in the distributions of the definite and unknown exposure groups was not significant ($p=0.35$). The same pattern of significant differences in distributions was noted between the exposure groups for SEM fibre analyses. A comparison between PCM and

SEM asbestos fibre counts per exposure group revealed a significant difference in distributions ($p<0.05$ using the non-parametric Wilcoxon matched-pairs sign rank test[34]) in all exposure categories except definite exposure ($p=0.15$).

Table 3.5: Fibre concentrations by exposure category

Exposure category [a]	n[b]	Fibre concentrations	
		Phase Contrast Microscopy[c]	Scanning Electron Microscopy[d]
		Median (Range)[e]	Median (Range)[e]
Definite	32	147 174 (0 – 1 326 654)	184 925 (0 – 2 307 271)
Probable	44	44 851 (0 – 552 955)	0 (0 – 512 349)
Possible	16	44 177 (0 – 411 630)	0 (0 – 1 706 336)
Unlikely/none	96	76 150 (0 – 2 333 515)	0 (0 – 7 527 368)
Unknown	7	389 887 (51 769 – 4 801 414)	0 (0 – 4 584 432)
Total	195	79 308 (0 – 4 801 414)	0 (0 – 7 527 368)

[a] See Table 2.1 for definition of exposure categories
[b] n = number of cases per exposure category
[c] PCM – all fibres are counted
[d] SEM – asbestos fibres are counted
[e] Reported as fibres/g dry lung tissue

3.2.2 Asbestos bodies

On PCM, 55 cases (28%) had any asbestos bodies detected where all had raised concentrations (≥1 000 bodies/g dry tissue). While SEM is not recommended for counting asbestos bodies in lung tissue (Table 1.2), bodies were counted at the same time as fibres. SEM detected asbestos bodies in 22 cases (11%) where all had raised concentrations.

Figure 3.3 shows the distribution of PCM-determined concentrations of asbestos bodies in 195 cases. The concentrations range from 0 to 651 213 bodies/g dry lung tissue and follow a positively skewed distribution, shown by the normal density plot (red).

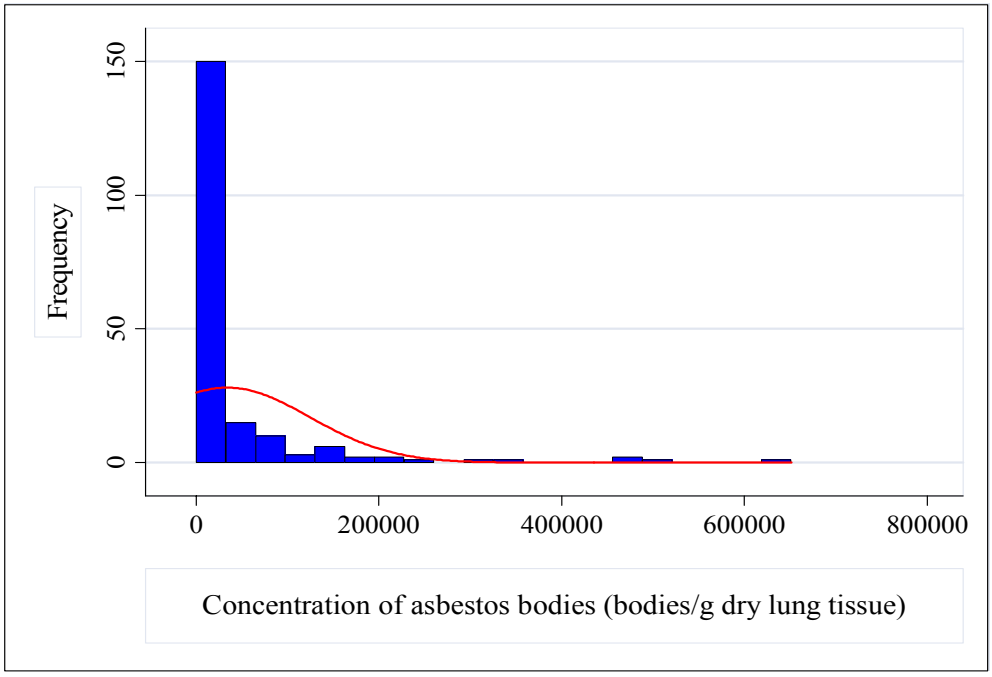


Fig 3.3: Distribution of concentrations of asbestos bodies, determined by PCM

SEM analyses (Fig 3.4) for asbestos bodies revealed a similarly positively skewed distribution of concentrations but with a much wider range of concentrations (0-2779189 bodies/g dry tissue), compared to PCM-determined concentrations.

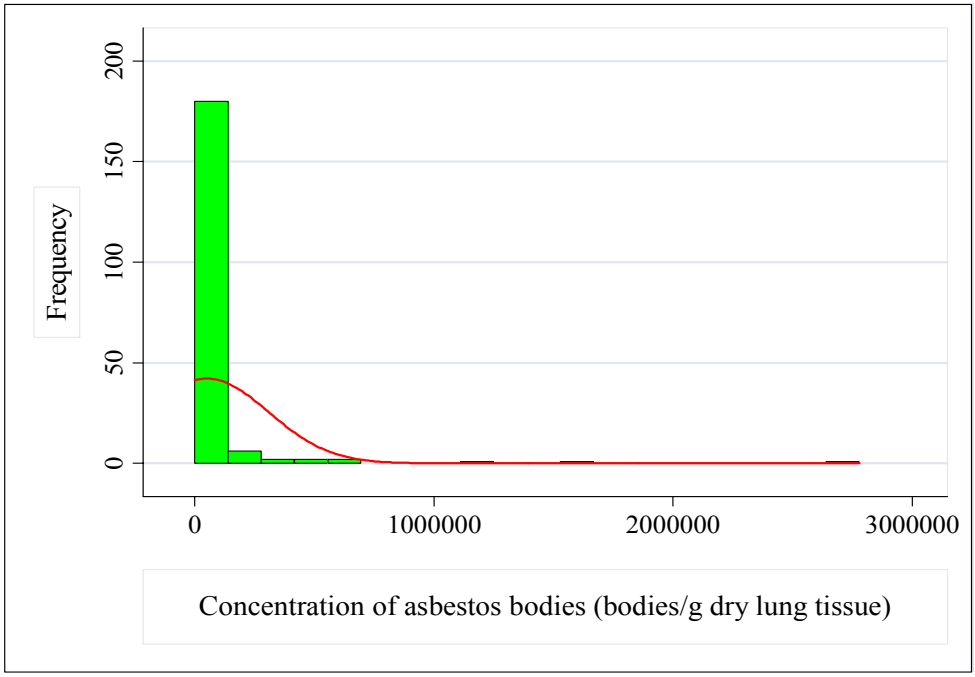


Fig 3.4: Distribution of concentrations of asbestos bodies, determined by SEM

The distributions of asbestos body concentrations, per exposure category, determined by phase contrast and electron microscopy are compared in Table 3.6. Because 72% of the 195 cases had no asbestos bodies detected by PCM, most exposure groups had median values of zero. Similarly, because 89% of cases had no bodies detected by SEM, all exposure categories had median values of zero.

Table 3.6: Asbestos body concentrations by exposure category

Exposure category [a]	n[b]	Asbestos body concentrations	
		Phase Contrast Microscopy	Scanning Electron Microscopy
		Median (Range)[c]	Median (Range)[c]
Definite	32	50 167 (0 – 485 185)	0 (0 – 597 648)
Probable	44	0 (0 – 158 960)	0 (0 – 63 172)
Possible	16	0 (0 – 50 599)	0 (0 – 568 779)
Unlikely/none	96	0 (0 – 651 213)	0 (0 – 2 779 189)
Unknown	7	19 196 (0 – 165 654)	0 (0 – 1 180 839)
Total	195	0 (0 – 651 213)	0 (0 – 2 779 189)

[a] See Table 2.1 for definition of exposure categories
[b] n = number of cases per exposure category
[c] Data reported as bodies/g dry lung tissue

By the non-parametric Wilcoxon rank sum test[34], the body concentrations of cases in the definite exposure category was significantly higher ($p<0.05$) than all except the unknown exposure category ($p>0.05$) by both PCM and SEM analyses (Table 3.6). Comparing PCM to SEM asbestos body concentrations per exposure group revealed a significant difference in the distribution of values ($p<0.05$ using the non-parametric Wilcoxon matched-pairs sign rank test[34]) in the total, possible and unlikely exposure categories. The definite, probable and unknown exposure categories had similarly distributed PCM- and SEM-determined values ($p>0.05$).

3.3 Correlation of PCM and SEM for fibre analyses

The positively skewed distributions of asbestos fibre and body concentrations, shown in Figures 3.1 to 3.4, necessitated a log transformation, to normalise the distribution. These log-transformed values were used to determine the strength of the association, if any, between SEM and PCM asbestos fibre and asbestos body analyses.

Figure 3.5 is a scatterplot of log-transformed PCM and SEM fibre concentrations. A bi-modal distribution at the higher end of the log scale is noted. A correlation co-efficient (r) of 0.3 ($p<0.00$) reveals a weak but significant association between PCM and SEM fibre concentrations.

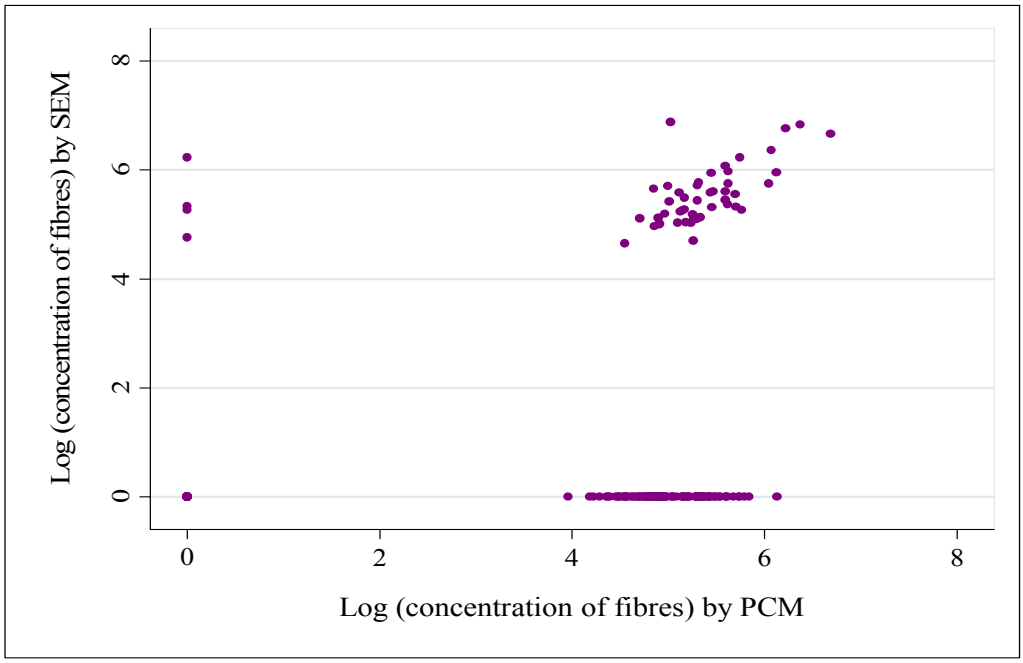


Fig 3.5: SEM vs PCM log-concentrations of fibres

The scatterplot of log-transformed PCM and SEM concentrations of asbestos bodies (Fig 3.6) shows a similar distribution to that in Figure 3.5, but the higher correlation co-efficient of 0.53 ($p<0.00$) suggests a strong, significant association between PCM and SEM concentrations of asbestos bodies in the lung.

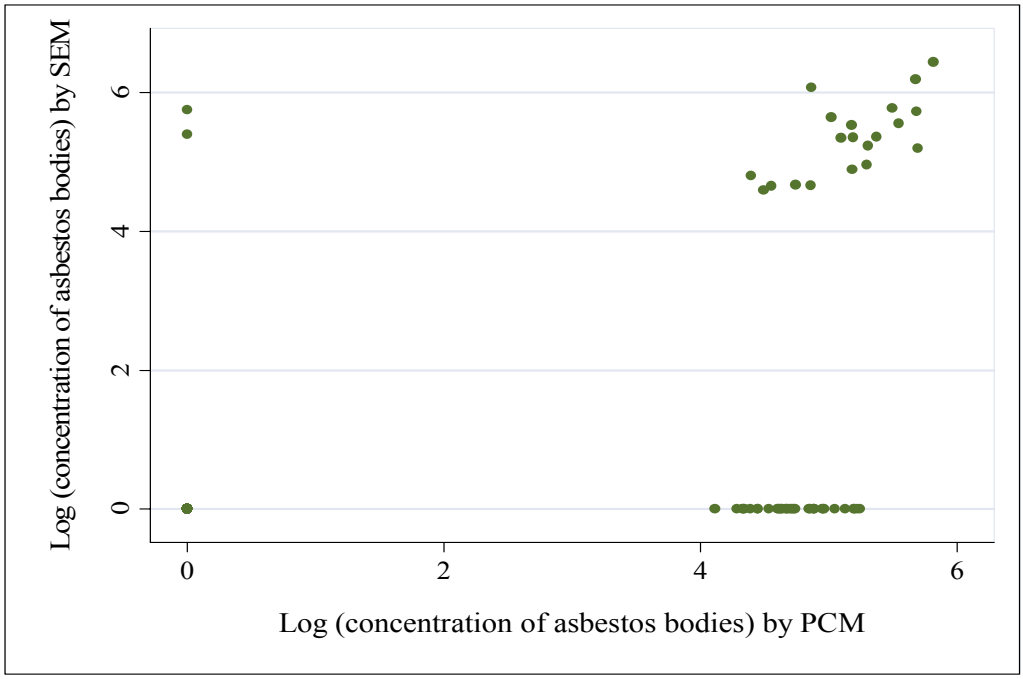


Fig 3.6: SEM vs PCM log-concentrations of asbestos bodies

3.4 Attribution of lung cancers using the Helsinki and NIOH criteria

All 195 cases were assessed to determine whether they were attributable using the two sets of criteria. Figure 3.9 depicts the attribution process (hierarchical system) and the number of cases that satisfied each of the criteria.

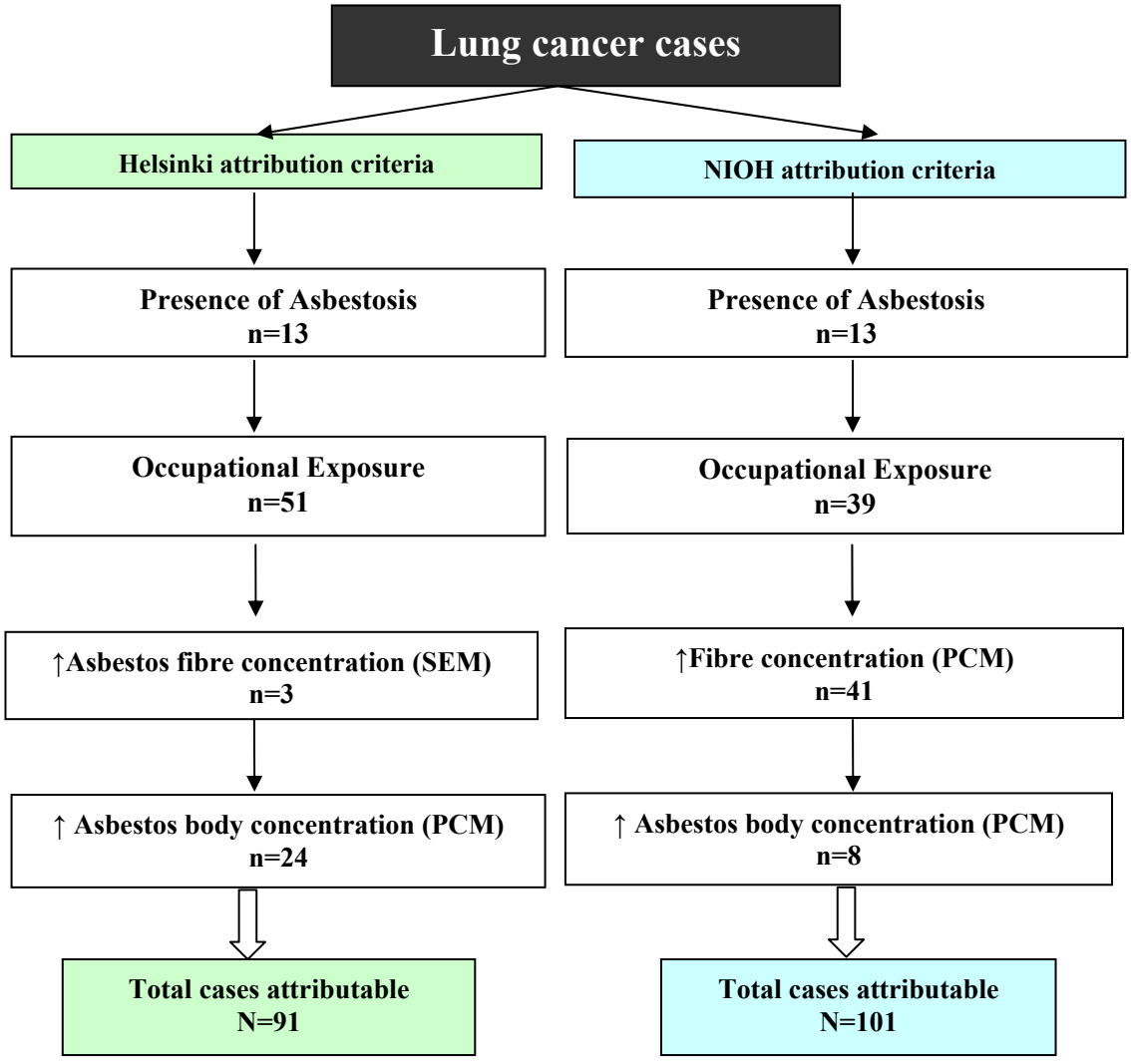


Fig 3.7: Attribution of lung cancers to asbestos exposure using the Helsinki and NIOH criteria

The Helsinki criteria found 47% (91) of the cases attributable to occupational asbestos exposure while the NIOH criteria found 52% (101) attributable. Asbestosis, a major marker of attributability, was present in 13 cases. Using this algorithm, SEM analyses contributed only three cases with raised asbestos fibre concentrations; one of these also had a raised asbestos body concentration.

A cross-tabulation of the number of NIOH- and Helsinki-attributable cases satisfying combinations of criteria by exposure category is presented in Tables 3.7 and 3.8, respectively.

Table 3.7: Distribution of NIOH-attributable cases by exposure category

Combinations of NIOH Criteria	Exposure Category					
	Definite	Probable	Possible	Unlikely	Unknown	Total
	n					
Asbestosis + occupational exposure + raised asbestos conc*	6	1	0	0	0	7
Asbestosis + occupational exposure	2	0	0	0	0	2
Asbestosis + raised asbestos conc*	0	0	0	1	3	4
Asbestosis only	0	0	0	0	0	0
Occupational exposure + raised asbestos conc*	18	15	0	0	0	33
Occupational exposure only	6	0	0	0	0	6
Raised asbestos conc* only	0	0	7	39	3	49
Not attributable	0	28	9	56	1	94

* Raised asbestos conc = raised fibre or raised body concentration as defined by the NIOH criteria

Of the 101 NIOH-attributable cases, in 49 attribution was made on the basis of raised asbestos burden in the lungs (Table 3.7). Among these, using the occupational exposure category there was possible exposure in 7 cases, unlikely exposure in 39 cases and unknown exposure in 3 cases. Furthermore, of the 7 cases with unknown occupational asbestos exposure, 3 (43%) had both asbestosis and a raised asbestos concentration in the lung.

Table 3.8 shows the distribution of Helsinki-attributable cases by exposure category. Of the 104 cases that were not attributable; by occupational history, 2 had definite exposure and 10 had probable exposure. These 12 cases did not satisfy the Helsinki criteria requirements for period of employment in these occupations. One-third (27) of the cases had raised asbestos concentrations only. Of these, 16 were in the unlikely exposure category and 3 had definite exposure but for less than one year. Similar to the NIOH-attributable cases, 3 cases with

unknown occupational histories had evidence of both asbestosis and raised asbestos concentrations in the lungs.

Table 3.8: Distribution of Helsinki-attributable cases by exposure category

Combinations of Helsinki Criteria	Exposure Category					
	Definite	Probable	Possible	Unlikely	Unknown	Total
	n					
Asbestosis + occupational exposure + raised asbestos conc*	5	1	0	0	0	6
Asbestosis + occupational exposure	2	0	0	0	0	2
Asbestosis + raised asbestos conc*	1	0	0	1	3	5
Asbestosis only	0	0	0	0	0	0
Occupational exposure + raised asbestos conc*	13	6	0	0	0	19
Occupational exposure only	6	26	0	0	0	32
Raised asbestos conc* only	3	1	6	16	1	27
Not attributable	2	10	10	79	3	104

* Raised asbestos conc = raised asbestos fibre or raised asbestos body concentration defined by the Helsinki criteria

3.5 Comparison of proportions of asbestos-attributable cases

The attributability of cases using the NIOH vs the Helsinki criteria is shown in Table 3.9. The proportion of concordant results was 72.3%, while 27.7% of the findings were discordant. Of the 54 discordant pairs: 32 cases were attributable by the NIOH criteria and not the Helsinki criteria; where 31 had raised fibre counts by PCM and 1 had a history of asbestos mining for <1 year. Among the 22 cases attributable by the Helsinki criteria and not the NIOH criteria, 20 were employed in asbestos exposed populations for >5 years and 2 had raised asbestos fibre concentrations by SEM. Because of the inherent differences in methods of attribution between the Helsinki and the NIOH criteria (described in Section 1.7.3), a comparison of the two methods of assessment of attributability was performed (Table 3.9). The internationally derived Helsinki criteria were used as the gold standard for the comparison.

Table 3.9: Attributability of cases by the NIOH criteria compared to the Helsinki criteria

NIOH Attributable	Helsinki Attributable		Total
	Yes	No	
Yes	69	32	101
No	22	72	94
Total	91	104	195

Percent Concordance = 72.3%
Sensitivity = 75.82% (95% CI: 65.7-84.2)
Specificity = 69.23% (95% CI: 59.4-77.9)
Positive Predictive Value = 68.32% (95% CI: 58.3-77.2)
Negative Predictive Value = 76.60% (95% CI: 66.7-84.7)

The NIOH criteria correctly identified 75.82% (sensitivity) of the Helsinki-attributable cases and 69.23% (specificity) of the not attributable cases. The proportion of NIOH-attributable cases that were correctly identified as attributable was 68.32% (PPV) and the proportion of

NIOH non-attributable cases correctly identified was 76.6% (NPV). The Kappa statistic (κ) was used to measure the agreement between the two sets of criteria for determining attributability on the same population. It is defined as the "proportion of agreement after chance agreement is removed from consideration"[35]. Using the values in Table 3.9, a κ-statistic of 0.4475 (95% CI: 0.32 – 0.57) was calculated. This is an indication of fair agreement[36] between the two methods of determining attributability of lung cancer cases to occupational asbestos exposure.

3.6 Predictors of SEM-determined raised asbestos fibre concentrations

Conducting scanning electron microscopy analyses on cases with asbestos-related diseases is a costly and highly skilled technique and its use in developing countries like South Africa, where the prevalence of these diseases is high, is questionable. But, sensitive methods for determining attributability for compensation purposes are a necessity. Therefore, to determine possible predictors of SEM-determined raised asbestos fibre concentrations, logistic regression modelling was used. On bivariate analysis, the following independent variables were associated ($p<0.1$) with a SEM-determined raised concentration of asbestos fibres: presence of asbestosis, presence of asbestos plaques, presence of asbestos bodies by LM, raised concentration of asbestos bodies by PCM, and log-transformed asbestos body concentrations; some with very wide 95% confidence intervals around the odds ratio. These independent variables were included in a multivariate logistic regression model, with SEM-determined raised concentration of asbestos fibres as the dependent variable, using an automatic backward selection method. But, only 8 cases had positive outcomes, so the power of the analysis was low resulting in an imprecise model with extremely wide 95% confidence intervals around the odds ratios of significantly associated variables. Consequently, these results could not be used and are not presented.

4.0 DISCUSSION

For compensation purposes, attribution of miners' lung cancer cases to occupational asbestos exposure is complex in the presence of other occupational and non-occupational carcinogens. It requires extensive exposure information and implementing a set of standardised criteria.

In this study, two sets of attribution criteria were used to determine the proportion of lung cancer cases attributable to occupational asbestos exposure in 195 miners with lung cancer.

In the absence of an international set of criteria, the NIOH developed and has been using criteria for the attribution of lung cancer to asbestos exposure in miners since 1988. The Helsinki criteria[11] were developed in 1997 by a group of international experts with an emphasis on the Northern Hemisphere developed world perspective. Considering the age of the NIOH criteria, its similarities to the Helsinki criteria are striking; indicating the progressive nature of the NIOH.

This study found that of the 195 lung cancer cases, 47% were attributable to asbestos exposure by the Helsinki criteria and 52% by the NIOH criteria (Fig 3.7), with differences in proportions of some factors within the criteria. The proportions for occupational exposure differed because of different conditions applied within each set of criteria: NIOH criteria require either a history of asbestos mining or an asbestos-exposed occupation with evidence of a raised burden of asbestos in the lung; Helsinki criteria require heavy exposure for more than 1 year or moderate exposure for more than 5 years[10]. In this regard, the NIOH criteria are more stringent if the case had no asbestos mining history, resulting in a lower proportion NIOH-attributable cases by occupational exposure. However, the Helsinki criteria condition

requiring heavy exposure for more than one year may be too stringent for asbestos miners who could have experienced very high intensities of exposure sufficient to cause lung cancer, within as little as one month of employment.

Similarly, the difference in the proportions of NIOH- and Helsinki-attributable cases with raised asbestos fibre concentrations could be explained by the NIOH criteria requiring a fibre concentration of >125 000 fibres/g dry lung tissue measured by phase contrast microscopy (PCM) while the Helsinki criteria require >1 000 000fibres/g dry lung tissue measured by scanning electron microscopy (SEM), to determine raised fibre levels.

By the Helsinki criteria, the low number of cases (3) attributable due to raised asbestos fibre concentrations in the lung may have been influenced by any or all of the following factors: the specificity in identifying fibres as asbestos by SEM-EDS analyses, compared to PCM; the higher limit for determining raised asbestos fibre counts; and the higher proportion of cases allocated as attributable based on occupational exposure.

Differences in the proportion of NIOH- and Helsinki-attributable cases for raised asbestos body counts may be explained by the hierarchical method used, whereby only cases not attributable by the previous three levels of criteria were evaluated at this level. This resulted in more cases being available for evaluation by the Helsinki than by the NIOH criteria.

In the comparison of the two criteria for attributability of lung cancer to asbestos exposure the NIOH criteria had a sensitivity of 75.8% and a specificity of 68.3%, compared to the Helsinki criteria: NIOH criteria missed 24% of the cases and incorrectly classified 32%. Although the ideal would be that criteria are both highly sensitive and specific, a balance has

to be found bearing in mind the consequences of incorrect attribution. From the individual's point of view, attribution of the lung cancer to occupational asbestos exposure necessitates a high sensitivity to decrease the probability of missing any true positives; using the NIOH criteria, 22 asbestos-attributable lung cancers (by the Helsinki criteria) would not have qualified for compensation. From the economic burden point of view, where asbestos-attributable lung cancer payouts are costly, false positives need to be kept to a minimum; the NIOH criteria would have resulted in compensation being unnecessarily awarded to 32 miners resulting in an increased cost for compensation payouts.

Based on data from the literature, about 5-7% of all lung cancers are attributable to occupational asbestos exposure[10]. However, in specific asbestos exposed settings, reports of proportions of asbestos-attributable lung cancers have been higher. Among asbestos cement workers in Italy, Magnani and Leporati (1998)[37] reported an attributable risk of 67.5% in men. Among Swedish insulation workers, Järvholm and Sanden (1998)[38] reported an attributable risk of 50%. Our study did not determine a measure of association (attributable risk), but the proportion of cases found attributable to asbestos exposure ranged from 47-52% using the two sets of criteria.

Four studies using the Helsinki criteria found varying degrees of attributability depending on the populations studied and the factors of the Helsinki criteria applied. Bianchi *et al* (1999)[28] found that, in a population of mainly shipyard workers in Italy, 61% of the cases were attributable to asbestos exposure using occupational history and asbestos body concentration (as defined by the Helsinki Criteria). In a population of lung cancer cases selected from a TB and Pulmonology Institute in Hungary, Mandi *et al* (2000)[29] determined a 4% attribution fraction using fibre-years of exposure (as defined by the Helsinki Criteria). Both Roggli

(2000)[30] and Mollo (2002)[24] used only the presence of asbestosis to determine attributability, but their selection of different study populations resulted in vastly different attribution fractions of 82% and 6%, respectively. A limitation in these studies was the use of only one or two factors within the criteria, which could have led to an underestimation of the true proportion of asbestos-attributable lung cancers.

The present study differs considerably from the afore-mentioned in two ways. Firstly, we used all possible factors in the Helsinki criteria to determine attributability. Secondly, our study population consisted entirely of South African mineworkers with the probability of either primary or secondary exposure to asbestos. Therefore, the results from this study are relatively unique and should not be compared directly to other studies that used different methods or populations.

Cases with raised asbestos fibre burdens but with no history of occupational exposure and those with asbestosis and raised asbestos fibre burdens despite unknown occupational exposure showed the importance of supplementing occupational history with other tangible measures of asbestos exposure when attributing lung cancers to occupational asbestos exposure. Almost two-thirds of the asbestos attributable lung cancers in this case series had no history of asbestos mining, highlighting the importance of secondary exposure to asbestos in the mining industry.

PCM fibre counts are not recommended for asbestos fibre counts (Table 1.2) as it is relatively insensitive and non-specific for asbestos fibres, compared to SEM[39]. As a result the correlation between log-transformed SEM asbestos fibre concentrations and PCM fibre concentrations was significant, but very low (r=0.3). There were also significant differences

in the distributions of SEM- and PCM-determined fibre concentrations per exposure category. Therefore, attribution of cases where fibres were only detected on PCM, should be considered with caution as the fibres counted may not all have been asbestos.

Of interest was that of the 195 cases, on which SEM fibre counts were performed, eight cases had SEM-determined raised asbestos fibre concentrations but six of these also had other evidence indicating an asbestos-attributable lung cancer. Asbestos fibre counting by SEM is an expensive, labour intensive and highly skilled procedure that is not available in many parts of the developing world making the additional benefit of its use in attribution, in such localities, questionable.

While controversy over whether asbestosis serves as a precursor or marker of asbestos-related lung cancer has yet to be resolved, the Helsinki report asserts that "prevailing scientific evidence indicates that the asbestos fibre burden in lung tissue is the primary determinant for the development of lung cancer; within this context, asbestosis has significance primarily as a marker of a high fibre burden"[10], but asbestosis may also confer an extra risk of lung cancer beyond that of asbestos exposure alone[11]. Similarly, on the role of smoking in the attribution of lung cancer to asbestos exposure, the Helsinki criteria state that "although tobacco smoking affects the total lung cancer risk, this effect does not detract from the risk of lung cancer attributable to asbestos exposure". In this dataset, of the 82 cases who had ever smoked, 41.5% were also attributable to asbestos exposure by both sets of criteria. Therefore, to consider smoking as a sufficient etiologic explanation for the cancer, neglecting occupational history and asbestos burden in the lung would result in a gross underestimation of the proportion of lung cancers attributable to occupational asbestos exposure.

5.0 LIMITATIONS

In this study, data on the extent and type of asbestos exposure came from two sources: records of occupational history and burden of asbestos in the lung determined by microscopy. Each of these sources has varying degrees of reliability which could have led to an information bias.

Occupational histories ranged from no history (in 3 cases) to a very comprehensive history. The lack of reliability of occupational history alone, for attribution, was shown in cases with with raised asbestos fibre burdens and no indication of occupational exposure by work history. These anomalies could also be explained by environmental asbestos exposure and asbestos-related occupations held outside the mining industry. Alternatively, the list of asbestos-exposed occupations used may not have been comprehensive enough to detect all occupationally exposed cases. Furthermore, classifying exposure histories into moderate or heavy exposure, as recommended by the Helsinki criteria, is difficult because of varying conditions in different mines and changes in working environments over time.

The burden of retained asbestos in the lung, while more objective than an occupational history, is also subject to limitations. Fibres and bodies were counted in a 1ml aliquot of 50ml of processed tissue. The use of only 2% of the sample could have introduced a sampling bias, but researchers at the NIOH previously found that examining the entire 50ml sample was not effective when looking at the lungs of miners, because the high concentration of other inorganic dusts (e.g. silica) present in the tissue sample limited visibility. However, the standard calculations for translating counts into concentrations (Appendix B) had to be adjusted to account for the 1:50 sample count, resulting in concentrations of fibres that were either 0 or more than 20 000 fibres/g dry tissue. This was

reflected in a bi-modal distribution of log-concentrations of fibres and bodies which is not comparable to the log-normal distributions reported from other studies[30]. This methodology may also have led to more cases with raised fibre burdens in the lung and could thereby affect attributability.

Asbestos burden analyses also lack accuracy in reflecting past exposure to non-amphibole asbestos: these fibres tend to fragment into smaller fibres that can either be cleared from the lung or be chemically digested thus leading to lower retention of fibres in the lung[9].

Two forms of selection bias may have influenced this study's results. The first was that 23 lung cancer cases did not have tissue specimens sent for fibre analysis. Compared to the 195 cases included in the series, these cases differed in that 78% were black miners whereas only 25% of the case-series was black. Two of the four pathologists employed at the time were responsible for 87% of these cases not having tissue sent for fibre analyses.

The second selection bias was that retired black miners are underrepresented in this population. Autopsy rates are as high as 80% for all miners who die while in employment and for white ex-miners, but are much lower in black ex-miners[27]; they usually reside in rural areas without the facilities for submitting cardio-respiratory organs to the NIOH for autopsy[40]. This may account for the significant difference in mean ages of 67 for white and 52 for black miners, in this study.

6.0 CONCLUSIONS

Despite the limitations of the study, five issues in the attribution of lung cancers to occupational asbestos exposure in miners have been highlighted: 1) the two sets of criteria identified similar proportions of asbestos-attributable lung cancers with concordance of 72%; 2) secondary asbestos exposure is important as a high proportion of non-asbestos miners had an asbestos-attributable lung cancer; 3) the proportion of NIOH-attributable cases may be overestimated due to the use of phase contrast microscopy, rather than the more specific scanning electron microscopy, to count asbestos fibres; 4) applying as many factors as possible, within the criteria, increases the probability of correct attribution in cases with incomplete information; 5) in developing countries the cost of expensive SEM fibre counts may outweigh the benefits.

7.0 RECOMMENDATIONS

7.1 Microscopy

Most laboratories push the entire 50ml sample through a filter which is used for counting. At the NIOH, we only push 1ml through the filter and count. This is because most miners are exposed to other dusts which are not removed during the washing process. This process can lead to a sampling bias as mentioned in the limitations (Chapter 5.0).

The following is recommended to reduce the sampling bias:

- Count at least 3 slides of 1ml samples and average the counts of asbestos fibres seen on SEM and asbestos bodies seen on PCM;
- Count the entire filter rather than 100 fields for both PCM and SEM.

7.2 Attribution

Even though the κ-statistic determined fair agreement between the two sets of attribution criteria, based on the results from this study and the limitations of the NIOH and Helsinki criteria, it is recommended that the NIOH criteria be modified, as shown in Table 7.1. The occupational history should now include an asbestos-exposed occupation with ≥ 5 years of exposure. The method for determining raised asbestos fibre counts should be changed according to the above-mentioned recommendations.

Table 7.1: Recommended modified NIOH criteria

	Factors	Conditions
Recommended modified NIOH criteria	**Asbestosis**	Presence of pathology-diagnosed asbestosis
	Occupational History	History of working on an asbestos mine for any period or Asbestos-exposed occupation for ≥ 5 years
	Raised asbestos body concentration (PCM)	≥ 1 000 asbestos bodies/g dry lung tissue
	Raised asbestos fibre concentration (SEM)	≥ 1 000 000 asbestos fibres/g dry lung tissue

As defined in Table 2.3

The factors should be applied according to their order on the table in a hierarchical fashion: if a case has asbestosis, no further factors need to be investigated, if not the occupational history should be investigated; if not attributable by occupational history, asbestos body counts should be done, by PCM only; and only if this factor is not satisfied for attribution should SEM asbestos fibre analyses be performed. This will reduce the need to perform SEM fibre analyses. For the 195 lung cancers used in this study, this method attributes ~48% of the cases to asbestos exposure and would have necessitated SEM fibre analyses on about half of the cases.

7.3 Measures of association

Based on the limitations of both the NIOH and Helsinki criteria, it is recommended that the afore-mentioned recommended modified NIOH criteria should be used for the calculation of future measures of associations.

7.4 Funding for microscopy analyses

Because of the high cost of SEM analyses, it is recommended that the Compensation Commissioner be approached for funding to conduct SEM analyses on all cases. This sponsorship would be to their advantage as it would aid in ensuring that the correct cases are being put forward for the limited compensation funds that are available and also limit the number of erroneous payouts.

8.0 APPENDICES

8.1 Appendix A – Merged database variables

Variable	Original Database	Description
pnumber	both	Pathology case number
bureauno	aut	Bureau no
burnum	fc	Bureau no
emnum	fc	EM number
reportst	aut	Type of autopsy
pathyr	fc	Pathology year (from pnumber)
year	fc	Microscopy year (year tissue from case went for microscopy)
age	fc	Age at death
gender	fc	Sex
race	fc	Race
popcode	aut	Race
birth	aut	Date of birth
death	aut	Date of death
pathcode	aut	Pathologist code
lungca	fc	Confirmed lung cancer case
codcert1-3	aut	CoD on Death certificate
codpath1-3	aut	CoD by pathology
pathcod1-3	fc	CoD by pathology
asbestosis	fc	Presence of asbestosis
asbplaq	fc	Presence of asbestos plaques
islets	fc	Presence of islets
fbpath	fc	Ferruginous body pathology
comments	fc	Additional comments on pathology diagnosis
eversmoke	fc	Did the case ever smoke?
asbexp	fc	Asbestos exposed wrt occ and mine
occ1	fc	Occupation 1st worked at if asbexp=yes
occ2	fc	Occupation 2nd worked at if asbexp=yes
occ3	fc	Occupation 3rd worked at if asbexp=yes
occ4	fc	Occupation 4th worked at if asbexp=yes
mine1-4	fc	Mine worked at per asbestos-exposed occupation
occst1-4	fc	Occ start date per asbestos-exposed occupation
occend1-4	fc	Occ end date per asbestos-exposed occupation
commodity1	fc	Commodity case was exposed to for longest
dur1	fc	Duration exposed to commodity1
lastmine	fc	Last mine case worked at
yrstart	fc	Year mining occupation started
yrend	fc	Year mining occupation ended
yearstar	aut	Year mining occupation started
yearend	aut	Year mining occupation ended

wetwtdig	fc	Digestion wet weight
drywtref	fc	Reference dry weight
wetwtref	fc	Reference wet weight
lmfield	fc	# of fields counted on LM
lmfib	fc	# of Fibres counted on LM
lmfibdry	fc	Concentration of fibres (/g dry weight)
lmfibwet	fc	Concentration of fibres (/g wet weight)
lmbodies	fc	# of Bodies counted on LM
lmboddry	fc	Concentration of bodies (/g dry weight)
lmbodwet	fc	Concentration of bodies (/g wet weight)
malislno	aut	Islets (number)
maltucen	aut	Lung tumour central
maltuper	aut	Lung tumour peripheral
mapasbl	aut	Asbestotic plaques – left lung
mapasbr	aut	Asbestotic plaques – right lung
milferb	aut	Ferruginous bodies and fibrosis
milsili	aut	Silicotic islets
smfield	fc	# of fields counted on SEM
smfib1	fc	# of asbestos fibres counted
smfib1dry	fc	Dry concentration of asbestos fibres counted
smfib1wet	fc	Wet concentration of asbestos fibres counted
smfib2	fc	# of non-asbestos fibres counted
smfib2dry	fc	Dry concentration of non-asbestos fibres counted
smfib2wet	fc	Wet concentration of non-asbestos fibres counted
smbodies	fc	# of asbestos bodies counted
smboddry	fc	Dry concentration of asbestos bodies counted
smbodwet	fc	Wet concentration of asbestos bodies counted
smfibtot	fc	Sum of asbestos+non-asbestos fibres counted
smfibtotdry	fc	Dry conc asbestos+non-asbestos fibres counted
smfibtotwet	fc	Wet conc asbestos+non-asbestos fibres counted

aut = Autopsy database, fc = Fibre count database

8.2 Appendix B – Extract of NIOH Standard Operating Procedure (SOP) for microscopy methods

LUNG DIGESTION

In this laboratory, 3 pieces of lung tissue from the upper, middle and lower lobes are received in formalin

1. The specimen is recorded in the EM register and given an EM number and a job card is filled in
2. A sample of tissue about 6- 10 grams is cut from each piece and rinsed in distilled water
3. Make foil baskets- tin foil folded over the top of the tube and folded round the tube – for weighing and drying
4. Each sample of lung is then cut in half and put into 2 foil baskets (one will be used for digestion and the other for the reference weight and dry weight)
5. Weigh both wet specimens and record on a standard form (Form 3) wet weights. Put reference weight specimen in the oven to dry overnight at 100^0C. Weigh dry specimen to obtain reference dry weight record (Form 3) weight and discard.
6. Pre filter the KOH using a polycarbonate 0.2µ filter.
7. Put the digestion specimen in a test tube and cover with KOH.
8. Digest for ±2 hrs in a water bath on high
9. Remove from water bath.
10. Add distilled water to near the top of the tube.
11. Mix well with a pipette before centrifuging at 1500 rpm for 30 mins to sediment the specimen
12. Remove the supernatant with a pipette, fill the tube with distilled water and spin again for 30 mins at 1500 rpm.
13. Pipette off the supernatant, fill to 10ml, with distilled water and pour into a crucible.
14. Ash the specimen by putting the crucible into the furnace cold and turn the Tº to 500^0C. (This is done in our laboratory by turning the dial on the furnace to 50%).
15. When correct temperature is reached switch off and let specimen and furnace get cold before taking the specimen out to make the filters for counting

FILTER PREPARATION

1. Loosen ashed specimen with drops of 15% HCl and pour back into the test tube and fill with filtered distilled water.
2. Agitate the specimen until resuspended
3. **For Light Microscopy**: Syringe 1ml of the solution, dilute with 4/5mls distilled water and pushed thru onto a MF- Millipore 0.45µ filter in a filter holder and dry in a closed petri dish for a day
4. Clear with Acetone fumes:
    a. Switch evaporator on at plug and wait for ready button to come on
    b. Fill the small evaporator syringe with acetone and put in the top of the clearer
    c. Write the EM number on the slide
    d. Put the filter upside down on the slide and put under the spout and push acetone fumes onto the filter to clear
    e. Dry for a couple of minutes and mount with glycerol triaceate
5. **For Scanning Microscopy**: Syringe 1ml of the solution, dilute with 4/5mls distilled water and pushed through onto a polycarbonate 0.2µ filter that is in a filter holder. The filters are then dried in a closed petri dish for a day.
6. Filters are mounted onto a carbon disk and coated in the sputter coater with gold for 1 ½ mins.

FIBRE COUNTING

A. LIGHT MICROSCOPY COUNTING

1. Cleared and mounted filters are counted on the phase contrast microscope.
2. The RTM1 counting rules for air-borne fibres apply although all fibres are counted.
3. The fibres counted are sized as follows:
    a. 1-5μm
    b. >5μm
4. 100 fields are counted at 500X magnification using a Walton-Beckett graticule.If there are many fibres, 50 fibres and a minimum of 50 fields are counted.
5. Asbestos/ferruginous bodies are counted simultaneously.
6. Record counts on standard Form 1.

B. SCANNING ELECTRON MICROSCOPY COUNTING

1. Filters are mounted onto a carbon disk and coated in the sputter coater with gold for 1 ½ mins.
2. They are then counted in the scanning electron microscope at 2000x magnification and a maximum of 100 fields are counted.
3. The counted fibres are sized and classified as follows:
    <5μ
    5-10μ
    >10μ
4. Asbestos/ferruginous bodies are counted simultaneously.
5. If few fibres are seen count up to 500 fields
6. If many fibres are seen do not exceed 100 fields or 100 fibres. But not less than 50 fibres.
7. Record counts on standard Form 2.

C. QUALITY CONTROL

Light Microscopy:

Slides that have been counted numerous times and have a consensus count will be randomly introduced into the batch of slides for counting by the supervisor. The technologist's performance in counting these "known" slides will be recorded and monitored.

Scanning Microscopy:

This laboratory is a member of an international quality control programme, AIM (Asbestos in Materials), run by the HSL in the United Kingdom. Results on quality assurance specimens, supplied by the UK, are reported on a 3-monthly basis.

CALCULATION OF ASBESTOS FIBRE/BODY CONCENTRATION IN LUNG TISSUE[1]

LIGHT MICROSCOPY

$$\textit{Conc.}\text{: fibres/g dry tissue} = \frac{\text{fibre density x total effective filter area}}{\text{Wet weight of digested sample}} \times \frac{\text{ref wet weight}}{\text{ref dry weight}} \times 50^{*}$$

$$\text{Fibre density} = \frac{\text{\# fibres counted}}{(0.007854 \times \text{\# fields counted})}$$

Total effective filter area = $\pi r^2 = \pi(11)^2 = 380.13$

*1ml of a 50ml solution is sampled to be pushed through the filter

SCANNING ELECTRON MICROSCOPY

$$\textit{Conc.}\text{: fibres/g dry tissue} = \frac{\text{fibre density x total effective filter area}}{\text{Wet weight of digested sample}} \times \frac{\text{ref wet weight}}{\text{ref dry weight}} \times 50^{*}$$

$$\text{Fibre density} = \frac{\text{\# fibres counted}}{0.0030672 \times \text{\# fields counted}}$$

Total effective filter area = $\pi r^2 = \pi(11)^2 = 380.13$

*1ml of a 50ml solution is sampled to be pushed through the filter

[1] Roggli VL. In: Pathology of asbestos associated disease (2nd edition). Appendix, pp11-14.

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